Transplantation

Renal transplantation

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Present outcomes and future challenges

Renal transplantation is undoubtedly the treatment of choice for children with end stage renal failure. While great advances have been made in the field of renal replacement therapy, the provision of dialysis and associated therapies places major restrictions on the child and their family. Poor weight gain and linear growth may necessitate supplementary feeding and/or recombinant growth hormone, and further dietary restrictions are imposed by the potassium and phosphate restricted diets that are necessary. Children also require oral and subcutaneous drug therapy for the treatment and prevention of anaemia, renal osteodystrophy, and hypertension. Psychomotor development is retarded and this is compounded by the imposition on normal childhood activities and interference with schooling associated with haemodialysis and, to a lesser extent, peritoneal dialysis.

The restoration of normal or near normal renal function by transplantation allows a number of these difficult and time consuming therapies to stop and may facilitate better growth and neurodevelopment. Furthermore, adult data clearly show transplantation to be more cost effective and associated with a reduction in long term mortality and improvement in quality of life compared with long term dialysis.[1]

In 2001, a total of 136 kidney transplants were performed in paediatric recipients (defined as under 18 years of age) in the United Kingdom, representing 8.1% of kidney transplants performed overall. This editorial reviews the current status of paediatric renal transplantation and explores the prospects for the future.

ORGAN DONATION AND ALLOCATION

At present, around 75% of UK paediatric transplants are performed using organs from both adult and paediatric cadaveric donors. The cadaveric organ donation rate in the UK in 2001 was 13.1 per million population (pmp) representing a total of 777 donors. This rate of donation, which has been relatively stable over recent years, is one of the lowest in Europe. In nations such as Spain, where specific national efforts have been made to improve donation rates, these have risen significantly (32.5 pmp in 2001),[2] and cadaveric donation rates are also higher in countries such as Belgium which have adopted an opt-out (presumed consent) system of organ donation.[3] The number of potential recipients for these organs is steadily increasing, the active kidney waiting list for the UK having risen from 3765 in 1992 to 5043 in 2002.

United Kingdom Transplant (UKT, www.uktransplant.org), through its advisory groups and annual directors meeting provides forums for agreeing rules for the allocation of cadaveric organs, and coordinates and audits the national allocation scheme. Organs are allocated on the basis of HLA matching, with organs being offered to the patient on the waiting list with the smallest degree of HLA mismatch to the donor. The current allocation algorithm gives priority to paediatric recipients for all 0,0,0* mismatched and all favourably matched (maximum of one mismatched antigen at either the HLA-A or HLA-B locus or at both, denoted by 1,0,0, 0,1,0, or 1,1,0) cadaveric organs, irrespective of whether the donor is paediatric or adult. This arrangement was agreed in view of the facts that HLA matching in paediatric patients was found to be significantly poorer than in adults, and that there are great difficulties associated with maintaining dialysis access and optimising growth in small children with end stage renal failure, necessitating early transplantation. As the paediatric recipient pool is relatively small, the net impact of this preferential allocation on the adult renal failure population has been shown by computer modelling to be minimal.

LIVING DONOR TRANSPLANTATION

Twenty five per cent of paediatric renal transplants performed in the UK in 2001 were from living donors. This figure has steadily risen over recent years, though living donation rates are still significantly lower than those reported from the Nordic countries (80%) and North America (55%). Living donor transplantation results in superior graft survival compared with cadaveric transplantation, and the procedure offers families the opportunity to plan for the date of transplantation. There are additionally psychological benefits associated with donation.[4] For paediatric recipients, the donor is most frequently a parent, though other adult relatives may be used provided that the HLA match is satisfactory; UK law prohibits the donation of solid organs by minors. The perioperative risk to the donor is small, reported mortality rates being 0.03% to 0.06%, and long term follow up studies of donors suggest that nephrectomy results in no excess long term morbidity or mortality.[5] The development of laparoscopic donor nephrectomy will hopefully further reduce the incidence of short term donor complications.[6] Living donation should only be undertaken in specialist centres as part of a properly planned programme; guidelines have recently been published by the British Transplantation Society.[7]

TRANSPLANTATION BEFORE DIALYSIS (PRE-EMPTIVE TRANSPLANTATION)

While most children undergo transplantation following the commencement of dialysis, transplantation prior to this (pre-emptive transplantation) results in improved growth and psychosocial development, and conserves peritoneal and haemodialysis access for future use in childhood or adult life. Furthermore, the long term outcome for pre-emptive transplants, which accounted for 20% of those performed in UK paediatric recipients in 2000, may be superior to that of transplants performed in children established on dialysis.[8 9] A child is generally considered for pre-emptive transplantation once the glomerular filtration rate (GFR) has fallen below 10–15 ml/min/1.73 m^2, and dialysis is anticipated within 18–24 months and/or a significant complication of renal failure is present, for example, growth failure. With very young or small children, the clinician and family have to consider the balance between the benefits of pre-emptive transplantation, the particular difficulties associated with the provision of dialysis (access problems, poor developmental outcome, etc), the increased early graft loss associated with transplantation in this high risk population (see below), and the surgical and immunosuppression related complications of transplantation.

RESULTS OF RENAL TRANSPLANTATION IN CHILDREN ARE IMPROVING

Registries held by UKT in the United Kingdom and the North American Pediatric Renal Transplant Cooperative Study

*Organs are classified according to the level of mismatching with the donor at the HLA-A, B, and DR loci. An organ with one mismatch at A, though none at B or DR is denoted a 1,0,0 mismatched organ.

(NAPRTCS) and the United Network of Organ Sharing (UNOS) in North America provide good quality data on long term graft survival. A recent analysis of 1252 cadaveric transplants performed in paediatric recipients in the UK between 1986 and 1995 showed a statistically significant improvement in graft survival with time (fig 1), with patients transplanted in 1993–95 achieving one year graft survival of 79% and five year graft survival of 68%.[10] Similar improvements with time have been reported by NAPRTCS, five year graft survival rates being 73% for cadaveric and 81% for living donor recipients transplanted between 1993 and 1995.[11] No single factor can be identified as the source of this improvement in graft survival and while it is tempting to speculate that this has occurred as a result of improved surgical techniques or immunosuppressive therapy, this may not be the case. In the UKT report, the improved graft survival observed between the 1986–90 and 1991–95 cohorts was shown by multifactorial analysis to be explained by the reduction in the use of kidneys from very young donors and the improved HLA matching which occurred over this time period.

FACTORS INFLUENCING GRAFT OUTCOME

The UKT[10] and North American[12 13] registries have both, using a variety of statistical methodologies, shown a number of different factors to adversely affect graft outcome.

Young donor age has been shown to be associated with increased early graft loss and inferior long term graft survival, particularly when such kidneys are used in small recipients, and organs from children under 5 years of age are no longer routinely offered for transplantation into children by UKT. Much of the poor outcome relates to a high incidence of vascular thrombosis and primary graft non-function. These organs are, however, offered for use en-bloc in adult patients meeting certain age, weight, and other criteria.

Young recipient age is also associated with a poorer short term graft survival compared with results obtained in older children and adults. This relates to a high incidence of vascular thrombosis and technical complications and a higher incidence of acute cellular and vascular rejection in this population. In the longer term, the age effect if reversed, with increased rates of graft loss among adolescents. The factors accounting for this are not identified, but almost certainly include non-compliance (fig 2).

Cold ischaemia time refers to the time that the harvested organ is stored in ice having been perfused with organ preservation fluid. Graft outcome deteriorates with increasing storage time, the risk of graft failure at three months post-transplantation increasing by 4% with each additional hour of cold ischaemia time.[10]

It is well established that *poor HLA matching* results in both a reduction in long term graft survival and an increased risk of immunological sensitisation (anti-HLA antibody production) following loss of a graft which reduces the number of potential donor organs suitable for future retransplantation. The UKT study showed that 0,0,0 mismatched and favourably matched kidneys were associated with the best transplant outcome,[10] confirming the findings of large adult registry series.[14] Because of these clear benefits of good HLA matching, it is now a national standard that UK paediatric transplant centres achieve at least 60% of transplanted kidneys being 0,0,0 mismatched or favourably matched, despite the fact that this will almost invariably result in a small increase in waiting time for a cadaveric organ.[15]

Ethnicity has been shown to be a major risk factor for the development of end stage renal failure in the UK, Asian children having a take-on rate for renal replacement therapy of 23.4 pmp compared with 6.6 pmp in White children.[16] No effect of ethnicity could be found in the UKT analysis,[10] in contrast to NAPRTCS data, which have consistently shown African-American race to be associated with inferior long term graft survival.

GRAFT FAILURE AND PATIENT MORTALITY

While the short and long term outcomes of transplantation continue to improve, graft failure remains a substantial problem. The rate of graft loss is highest in the first year following transplantation (fig 1), the majority of these kidneys being lost in the first month or two from vascular events and acute rejection. Thereafter, the rate of graft loss slows. Of the 582 grafts that had failed in the UKT analysis and the 1592 grafts that were lost in the NAPRTCS series (1987 onwards), rejection was the commonest cause of graft loss, accounting for 50.4–55% of all losses (acute rejection 19.3% and chronic rejection 31.1% in the NAPRTCS series). Vascular thrombosis was responsible for 10–12.8% of all losses, the majority of these occurring in the immediate post-transplant period; 7–9.5% of losses occurred due to death with a functioning transplant.[10 11]

The overall mortality rate in the 12th Annual NAPRTCS report was 6.5% in the first five years post-transplantation, infection and cardiopulmonary events being the commonest causes of death in both this and the UKT series. It is becoming increasingly apparent that cardiovascular disease, which is the cause of death in a large proportion of adult kidney recipients,[17] is also a very significant problem in the paediatric and young adult population.[18]

IMMUNOSUPPRESSIVE THERAPY

For the past two decades, cyclosporin based triple therapy (cyclosporin in conjunction with azathioprine and corticosteroids) has been the mainstay of immunosuppressive therapy for children undergoing renal transplantation. Over recent years, there has been a proliferation in the number of newer agents available, and many of these, including

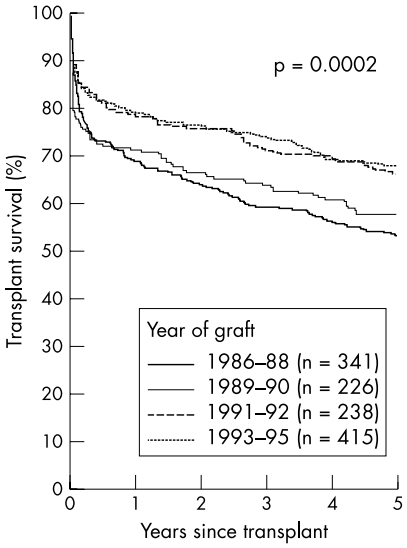

Figure 1 UK paediatric renal transplant survival by year of transplantation. Reproduced from Postlethwaite *et al*[10] with permission from Blackwell Munksgaard.

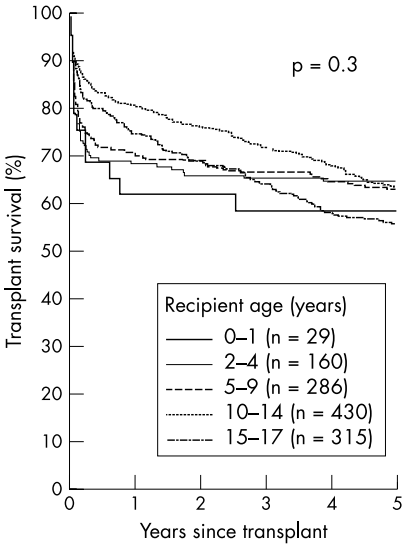

Figure 2 UK paediatric renal transplant survival 1986–95 by recipient age. Reproduced from Postlethwaite *et al*[10] with permission from Blackwell Munksgaard.

tacrolimus, mycophenolate mofetil (MMF), sirolimus (rapamycin), and the anti-CD25 monoclonal antibodies basiliximab and daclizumab have entered routine use in Europe and North America.[19] In general, these newer agents have more potent immunosuppressive activity than their older counterparts. While this may reduce the incidence of rejection, the risk of infection (particularly cytomegalovirus and Epstein-Barr virus), post-transplant lymphoproliferative disease and other malignancy may also be increased, and it is therefore essential that these drugs are thoroughly evaluated in children prior to their widespread adoption into routine clinical use.

Tacrolimus is the only new immunosuppressive agent to have been investigated in children in the context of a prospective randomised controlled trial (RCT). Children treated with tacrolimus based triple therapy were shown to have a reduced incidence of acute rejection and a significantly improved GFR at one year post-transplantation compared with those treated with cyclosporin based therapy.[20] Further follow up of this study has shown these early benefits of tacrolimus being translated into significantly improved graft survival at two years post-transplantation[21] (fig 3). The incidence of serious side effects of immunosuppressive therapy, most notably diabetes mellitus and malignancy, were not different between the two groups.

Much of the other literature relates to uncontrolled reports of the use of various regimens or comparisons with historical control groups; the latter studies need to be interpreted in the light of the improved graft survival that may have occurred with time alone. Uncontrolled studies of MMF,[22] basiliximab,[23 24] and everolimus[25] have shown low rates of acute rejection, though these need confirmation and further investigation in the context of prospective RCTs, a number of which are currently ongoing in Europe and North America.

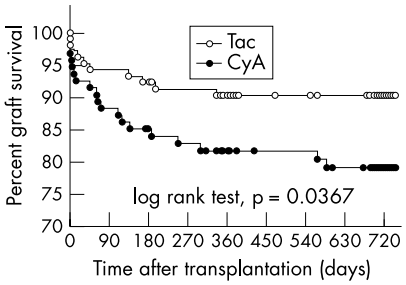

Figure 3 Graft survival in tacrolimus and cyclosporin treated patients in a large European prospective randomised controlled trial comparing triple immunosuppressive therapy with either tacrolimus or cyclosporin in conjunction with steroids and azathioprine. Tac, tacrolimus; CyA, cyclosporin. Reproduced from Filler *et al*[21] with permission from Elsevier.

Preliminary reports from centres using steroid-free immunosuppression in children appear promising, with very low acute rejection rates and excellent short term graft and patient survival, though steroid freedom came at the expense of the use of relatively intensive non-steroid immunosuppressive therapy with tacrolimus, MMF/sirolimus, and prolonged anti-CD25 therapy.[26] The avoidance of steroids was associated with a marked improvement in growth compared with historical controls treated with steroids. Improved growth is also seen with conversion to an alternate day steroid regimen[27] and with steroid withdrawal,[28] though the latter has been reported to result in an increased incidence of acute rejection.[29]

As is common in many childhood chronic conditions, compliance with medication is a major problem in transplanted patients, the problem being greatest among the adolescent population.[30] Non-compliance with immunosuppressive therapy is the commonest cause of late graft loss,[31] with 15–16% of children losing their graft because of this.[32 33] The problem appears to be greatest with those medications which are complex to administer or are associated with adverse side effects. Cosmetic side effects, particularly the Cushingoid facies and acne induced by corticosteroids, and the hypertrichosis and gingival hyperplasia induced by cyclosporin, are a particular source of distress to some children and are known to be linked to an increased rate of non-compliance. Despite the major clinical and economic implications of non-compliance, this remains a vastly under-researched and under-resourced area of medicine.

CHALLENGES FOR THE FUTURE

The great disparity between the supply and demand for donor organs poses a great challenge for all involved in transplantation. Much thought has been given to ways in which the donation rate in the UK might be increased.[34 35] The Department of Health has recently given UKT the responsibility of increasing the organ donation and transplant rates. Specific projects are underway to try and maximise donation from heartbeating donors after death certified by brain stem testing, to extend organ retrieval from non-heartbeating donors to most areas of the country, and to increase the rate of living donor transplantation. The plans are ambitious and significant improvements in kidney transplant numbers are likely to take a number of years to achieve.

Substantial efforts need to be made to ensure that the outcome of transplanted kidneys continues to improve. This can be achieved by further increasing the use of living donor and favourably matched cadaveric organs, though the latter may be associated with a small increase in waiting time prior to transplantation. Other known risk factors for poor outcome should also be minimised: it is now a national standard that organ cold ischaemia times should be kept to within 24 hours, though the pressure on operating theatre time may make this a difficult goal to achieve without a substantial injection of resources. The aetiology and treatment strategies for acute vascular thrombosis remain poorly understood and much further work is required to allow this significant cause of graft loss to be minimised.

There has been a recent proliferation in the number of immunosuppressant agents available, and a number of further agents with significant promise are currently in phase 1 and 2 trials in adults. While it is essential that dedicated paediatric trials are performed to determine their safety, efficacy, and tolerability in children, improving graft survival and falling acute rejection rates mean that adequately powered trials are becoming increasingly difficult to perform in view of the large numbers of patients required. The holy grail of transplantation remains the development of regimens which induce immune tolerance, allowing immunosuppressive therapy to be completely withdrawn without the development of organ rejection. Xenotransplantation using transgenic pig kidneys has the potential to deliver an unlimited supply of organs; however, this promise has yet to translate into clinical application, despite substantial research efforts over the past decade. Many aspects of both acute and chronic rejection are at present unsolved, and there remain major concerns about possible transmission of porcine endogenous retroviruses and other infectious agents.

The advances in renal transplantation which have occurred over the past 10–20 years have resulted in a marked improvement in the short to medium term outlook for children with end stage renal failure. Attention must now focus on improving their long term outcome, about which there remains some uncertainty.

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NW has received lecture fees/honoraria and

conference expenses from Fujisawa, Novartis, Roche, and Imtix Sangstat. Clinical trials in paediatric renal transplant patients sponsored by Fujisawa and Novartis are currently ongoing in Manchester

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